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EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	PAPER NUMBER
1636	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/575,127	SHIE ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 August 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *120-138* is/are pending in the application.

4a) Of the above claim(s) *123-131 and 135-138* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *120-122 and 132-134* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 April 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Appendix I*.

DETAILED ACTION

Receipt is acknowledged of an amendment, filed 4/7/2006, in which claims 1-119 were cancelled, and claims 120-138 were newly added. Claims 120-138 are pending.

Election/Restrictions

Applicant's election with traverse of Group I in the reply filed on 8/4/2009 is acknowledged. Upon further consideration, the restriction between Groups I and II has been withdrawn.

The traversal is on the ground(s) that the single general inventive concept of claims 120-138 is the modulation of angiogenesis in a mammal using agents that modify the expression or activity of Related Transcriptional Enhancer Factor-1 (RTEF-1). The response asserts that Stewart fails to teach or suggest the methods of claims 120-134, the kit of claim 135 or the composition of claims 136-138. Specifically, the response asserts that Stewart does not teach or suggest a role for RTEF-1 in angiogenesis. The response acknowledges that Stewart describes the identification of the human RTEF-1 nucleic acid and polypeptide sequences and discusses the relationship of RTEF-1 to a related factor, Transcriptional Enhancer Factor-1 (TEF-1), which is involved in the regulation of muscle-specific gene expression.

This is not found persuasive because the technical feature linking the inventions of Groups I-VIII is that they all relate to RTEF-1 nucleic acid or polypeptide, which is taught by Stewart et al. Because the technical feature linking the inventions of Groups I-VIII does not define a contribution over the prior art, there is no special technical feature linking the Groups. Thus, the finding of lack of unity is proper.

Applicant asserts that the special technical feature linking the Groups is the modulation of angiogenesis in a mammal using agents that modify the expression or activity of RTEF-1. The first named invention uses RTEF-1 polypeptide or nucleic acid to modulate angiogenesis. This product is taught in the prior art by Stewart et al. The special technical feature of Group I (now rejoined with Group II and referred to jointly as Group I) is the stimulation of angiogenesis by the administration of RTEF-1 polypeptide or nucleic acid molecule. The special technical feature of Group III is the inhibition of angiogenesis by administering a composition that reduces the expression or activity of RTEF-1. The special technical feature of Group III is not shared with the special technical feature of Group I. The two groups have opposite effects (increasing vs. decreasing angiogenesis) and do not share the same method steps (administration of RTEF-1 polypeptide or nucleic acid vs. administration of an RTEF-1 inhibitor). The special technical feature of Group IV is identifying a candidate compound that increases RTEF-1 expression or activity. This special technical feature is not shared with Group I, because the screening assay of Group IV is not a method of making the compounds used in the method of Group I. The special technical feature of Group V is the identifying a candidate compound that increases angiogenesis by measuring angiogenesis. The special technical feature of Group V is not shared with Group I, because the screening assay of Group V is not a method of making the compounds used in the method of Group I. The special technical feature of Group VI is a vector encoding RTEF-1. This technical feature does not link Groups I and VI, because Stewart et al teach a vector encoding RTEF-1 (e.g., page 69, right column). This feature is not a contribution over the prior art. Therefore, it is not a special technical feature. The special technical feature of Group VII is an RTEF-1 polypeptide. This technical feature does not link Groups I and VII, because Stewart

et al teach RTEF-1 polypeptide (e.g., Figure 1). This feature is not a contribution over the prior art. Therefore, it is not a special technical feature. The special technical feature of Group VIII is a composition that reduces the levels or activity of RTEF-1. This special technical feature does not link Groups I and VIII, because the compounds of Group VIII are not used in the method of Group I.

The requirement is still deemed proper and is therefore made FINAL.

Claims 123-131 and 135-138 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 8/4/2009.

An examination on the merits of claims 120-122 and 132-134 follows.

Specification

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The abstract of the disclosure is objected to because it exceeds 150 words in length. Correction is required. See MPEP § 608.01(b).

The disclosure is objected to because of the following informalities:

1. Page 46, line 13, page 57, lines 12-13, and Figures 3B, 9, 10 and 13 contain sequences that are not referred to by the use of a sequence identifier. Where the description or claims of a patent application discuss a sequence that is set forth in the Sequence Listing, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application. It would be remedial to amend pages 46, 57 and the Brief Description of the Drawings to refer to SEQ ID NOs: 1-7.

2. At page 4, line 16, the term "picornavirus" is misspelled.

Appropriate correction is required.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See page 16, line 6.

The use of the trademark CRONEX (page 54, line 30) has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

The incorporation of essential material in the specification by reference to an unpublished U.S. application, foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference, if the material is relied upon to overcome any objection, rejection, or other requirement imposed by the Office. The amendment must be accompanied by a statement executed by the applicant, or a practitioner representing the applicant, stating that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter. 37 CFR 1.57(f).

The attempt to incorporate subject matter into this application by reference to GenBank Accession Nos. AAC50763, Q62296, and P48984 is ineffective because essential material may only be incorporated by reference to a U.S. patent or U.S. patent application publication, which patent or patent application publication does not itself incorporate such essential material by reference. For human RTEF-1 (AAC50763), it would be remedial to refer to SEQ ID NO: 7.

Claim Objections

Claim 134 is objected to because of the following informalities: the term "picornavirus" is misspelled. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 120-122 and 132-134 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims require the provision of a genus of RTEF-1 polypeptide variants and nucleic acid molecules encoding said variants, where the RTEF-1 polypeptide has angiogenic activity. Claims 120 and 122 require the RTEF-1 polypeptide to have at least 60% identity to the sequence of human RTEF-1 (Accession Number AAC50763), mouse RTEF-1 (Accession Number Q62296), or chick RTEF-1 (Accession Number P48984). Claims 121 and 132-134 require at least 80% sequence identity to the sequence of human RTEF-1 (Accession Number AAC50763), mouse RTEF-1 (Accession Number Q62296), or chick RTEF-1 (Accession Number P48984). The rejected claims thus comprise a set of polypeptides and nucleic acid molecules encoding the polypeptides that are defined by percent identity to amino acid sequences disclosed in a non-patent database, where the polypeptides must have angiogenic activity.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of a complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, and any combination thereof.

The specification defines the term "angiogenic activity" to mean "having the ability to increase angiogenesis by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or more than 100% relative to a control" (page 9, lines 22-24). At page 9, lines 24-32, the specification states the following with regard to determining angiogenic activity:

> Angiogenic activity may be determined in *vitro* by measuring, for example, endothelial cell proliferation, endothelial cell migration, endothelial cell survival, and tubule formation. Alternatively, angiogenic activity may be determined in *vivo,* by counting or staining vessels, or alternatively, by quantitating functional vessels, using the MATRIGEL® assay, corneal micropocket assay, hind limb ischemic model, and chick chorioallantoic membrane (CAM) assay. Preferably, in *vitro* assays measure endothelial cell proliferation or survival and preferred *in vivo* assays are the hind limb ischemic model and the corneal micropocket assay. For the purpose of determining claim scope, the preferred assay is hind limb ischemic model.

The specification describes the sequence of GenBank Accession No. AAC50763 as SEQ ID NO: 7. The specification does not disclose the sequences of GenBank Accession Nos. Q62296 and P48984.

The specification notes that regions of RTEF-1 that have structural significance for biological function include the DNA binding domain at the amino-terminal end of RTEF-1 as discussed in Ueyama et al (Journal of Biological Chemistry, Vol. 275, pages 17476-17480, 2000). The specification discloses that mutation of Ser 254, Ser 290, Ser 322 and Ser 358 relative to the human wild-type sequence results in loss of RTEF-1 phosphorylation via interaction with PKC and MAPK and concomitant loss of signaling ability (e.g., page 15, lines 7-10). Further, the specification indicates the presence of an STY domain at amino acids 299-358 of the human sequence (e.g., page 15, lines 10-11). Ueyama et al teach that the STY domain is a region rich in serine, threonine and tyrosine residues (e.g., page 17479, paragraph bridging pages

17479-17480). Ueyama et al teach that the STY domain confers responsiveness to α_1-adrenergic signaling, thereby allowing RTEF-1 to bind to an MCAT element in the promoters of genes upregulated by RTEF-1 (e.g., page 17476; page 17478, left column; Figures 1 and 3).

The prior art does not appear to offset the deficiencies of the instant specification in that it does not provide a structure/function correlation for RTEF-1 and angiogenic activity. While the prior art teaches the binding of RTEF-1 to MCAT elements, the present specification teaches that the FGFR and VEGF promoters, which are responsive to RTEF-1 and are responsible for angiogenic activity, are completely devoid of any MCAT element (e.g., page 22, lines 17-28). Ueyama et al teach that the DNA binding domain of RTEF-1 and TEF-1 are 100% identical (e.g., page 17476, right column; Figure 1). The prior art teaches that the DNA binding domain of TEF-1 is a TEA domain, which is highly conserved (Burglin, TR. Cell, Vol. 66, pages 11-12, July 1991). However, the presence of the STY domain and TEA domain are not sufficient to describe variants that retain angiogenic activity. The STY domain has been shown to be important for α_1-adrenergic signaling and binding of RTEF-1 to MCAT elements, yet the angiogenic activity of RTEF-1 appears to be independent of MCAT binding (specification, page 22, lines 17-28). Moreover, the presence of a conserved DNA binding domain is not sufficient to describe the alterations that can be made to the sequence while retaining the ability to specifically bind elements in the COX-2, VEGF, and FGFR1 promoters.

Even if one accepts that the examples described in the specification meet the claim limitations of the rejected claims with regard to structure and function, the examples are only representative of the wild-type, full-length sequences of human, mouse and chick RTEF-1, which would be expected to have angiogenic activity. The results are not necessarily predictive

of variants of these sequences that retain angiogenic activity. Thus, it is impossible for one to extrapolate from the few examples described herein those variants that would necessarily meet the structural/functional characteristics of the rejected claims.

There is no teaching in the specification or prior art of the 40% or 20% of the RTEF-1 sequences that can be varied while retaining the angiogenic activity of the protein. Further, there is no disclosed or art-recognized correlation between structure and function. Although one could envision proteins that meet the percent identity requirements, one of ordinary skill in the art would not be able to identify without further testing which of those proteins have angiogenic activity.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is now is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides and nucleic acid molecules, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation or identification. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18USPQ2d 1016.

Given the very large genus of RTEF-1 polypeptides and nucleic acid molecules encompassed by the rejected claims, and given the limited description provided by the prior art and specification with regard to a structure-function correlation or a representative number of species, the skilled artisan would not have been able to envision a sufficient number of specific embodiments that meet the functional limitations of the claims to describe the broadly claimed genus. Therefore, the skilled artisan would have reasonably concluded applicants were not in possession of the claimed invention for claims 120-122 and 132-134.

Claims 120-122 and 132-134 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of increasing angiogenesis in a mammal, and a method of treating or reducing hypoxia in a mammal, comprising administering to said mammal, within or adjacent to ischemic or hypoxic tissues, the RTEF-1 polypeptide of SEQ ID NO: 7, or a nucleic acid molecule encoding said polypeptide, does not reasonably provide enablement for systemic administration of RTEF-1 polypeptide or nucleic acid; the use of other RTEF-1 polypeptides; preventing hypoxia, the use of any polyoma vector; the use of a papilloma vector, or the use of a picornavirus vector. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of

experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: Claims 120-122 are drawn to increasing angiogenesis in a mammal. Claim 120 is drawn to the step of providing to the mammal a therapeutically effective amount of Related Transcriptional Enhancer Factor-1 (RTEF-1) polypeptide or a nucleic acid molecule encoding said polypeptide, where said RTEF-1 polypeptide has angiogenic activity and at least 60% sequence identity to the sequence of human RTEF-1 (Accession No. AAC50763), mouse RTEF-1 (Accession Number Q62296), or chick RTEF-1 (Accession No. P48984). Claim 121 limits the percent identity of the method of claim 121 to at least 80% sequence identity. Claim 122 requires the RTEF-1 polypeptide to be provided to the mammal by administering a cell, tissue or organ that contains the polypeptide in a therapeutically effective amount.

Claims 132-134 are drawn to treating, preventing, or reducing hypoxia in a mammal at risk for or experiencing hypoxia. Claim 132 is drawn to the step of providing to the mammal a therapeutically effective amount of RTEF-1 polypeptide or a nucleic acid encoding said polypeptide, where the RTEF-1 polypeptide has angiogenic activity and at least 80% sequence identity to the sequence of human RTEF-1 (Accession No. AAC50763), mouse RTEF-1 (Accession Number Q62296), or chick RTEF-1 (Accession No. P48984). Claim 133 requires the nucleic acid molecule to be an expression vector selected from the group consisting of a plasmid or a viral vector. Claim 134 limits the viral vector to one selected from the group consisting of an adenovirus, retrovirus, adeno-associated virus vector, herpes simplex virus, SV40 vector, polyoma virus vector, papilloma virus vector, picornavirus vector, and vaccinia virus vector.

The nature of the invention is complex in that the polypeptide or nucleic acid molecule must be delivered in an amount sufficient to increase angiogenesis, treat or reduce hypoxia, or prevent hypoxia.

Furthermore, the nucleic acid sequences of GenBank Accession Nos. AAC50763, Q62296, and P48984 are critical or essential to the practice of the invention, but not included in the claim(s) or disclosure. The GenBank Accession numbers refer to entries in an electronic database which is subject to change over time. The GenBank Accession number identifies the nature of the sequence and does not vary with the different versions of the actual sequence that may change over time. "Essential material" may be incorporated by reference, but only by way of an incorporation by reference to a U.S. patent or U.S. patent application publication, which patent or patent application publication does not itself incorporate such essential material by reference. In the instant case, the claims are, in effect, incorporating the sequence of the GenBank Accession numbers by reference to the entries in the electronic database. "While the prior art setting may be mentioned in general terms, the essential novelty, the essence of the invention, must be described in such details, including proportions and techniques, where necessary, as to enable those persons skilled in the art to make and utilize the invention." See MPEP 608.01(p) [R-3]. Accordingly, the reference to the GenBank Accession numbers does not provide the features (i.e., amino acid sequences) that are critical or essential to the practice of the claimed invention.

Breadth of the claims: The claims are very broad with respect to the manner of providing the RTEF-1: administration of protein, administration of nucleic acid, administration of cells, tissue or organs, where the administration is local or systemic. Further, the claims are broad with

regard to the sequence of the RTEF-1 polypeptide. The polypeptide may be a mammalian polypeptide, such as human RTEF-1 or mouse RTEF-1, or may be a non-mammalian polypeptide such as chick RTEF-1. Moreover, the polypeptide may be any variant with at least 60% or at least 80% identity to the sequences of Accession Nos. AAC50763, Q62296, or P48984. Claim 134 is broadly drawn to the use of any polyoma virus vector, any papilloma virus vector, and any picornavirus vector. The claims are also broad with regard to requiring the ability to treat or prevent hypoxia. The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims.

Guidance of the specification and existence of working examples: The specification discloses the sequence of human RTEF-1 as SEQ ID NO: 7. In preliminary studies, Applicant found that the expression of RTEF-1 was increased three-fold in endothelial cells cultured under hypoxic conditions. To confirm this observation, Northern blot analysis was performed to measure the time-dependent level of RTEF-1 mRNA in RNA isolated from bovine aortic endothelial cells (BAEC) cultured under hypoxic conditions (<1% O_2) (e.g., page 43, lines 15-20). Figures 1A and 1B show that RTEF-1 is induced by hypoxia and that such expression peaked about 6 hours following exposure to hypoxia. Further, it was demonstrated that RTEF-1 overexpression in BAEC cells by transfection of RTEF-1 cDNA resulted in the upregulation of VEGF expression (e.g., page 43, lines 22-28; Figures 2A and 2B). VEGF expression is induced by hypoxia, but is further induced by RTEF-1 (e.g., page 43, lines 26-28). Further, RTEF-1 was shown to enhance VEGF promoter activity under hypoxic conditions (e.g., page 47, lines 13-23; Figure 7). Based on these observations, Applicant proposed that RTEF-1 may play a role in

promoting the expression of VEGF by regulating its promoter activity, particularly in hypoxic conditions.

Using a promoter assay, Applicant determined that possible gene regulatory elements within the VEGF promoter necessary for RTEF-1 activation are located between -194 and -66 of the VEGF sequence (e.g., page 44, lines 16-18; Figures 2 and 3). This region of the VEGF promoter demonstrated a dose response increase in promoter activity with increasing amounts of RTEF- (e.g., paragraph bridging pages 44-45; Figure 4). Further mutation analysis identified the Sp1-I binding domain (-97 to -87) of the VEGF promoter as being required for the stimulation by RTEF-1 (e.g., pages 45-47).

Next, the ability of RTEF-1 to accelerate cellular proliferation and the formation of a vascular structure, via transactivation of VEGF, was tested in BAEC cells overexpressing RTEF-1. These cells demonstrated a faster growth rate compared with wild-type or vector transfected BAEC cells (e.g., page 48, lines 1-6; Figure 8). Further, ring and cord formation was visible in the RTEF-1 stably transfected BAEC but not in control cells after 48 hours of culture on growth factor-reduced Matrigel® (e.g., page 48, lines 7-11; Figure 8).

In addition to regulating the expression of VEGF, the specification demonstrates that RTEF-1 is capable of stimulating the expression of FGFR1 and COX-2. RTEF-1 overexpression increases FGFR1 promoter activity in BAEC cells (e.g., paragraph bridging pages 48-49). The promoter activity was localized to an SP-1-like element in the FGFR1 promoter (e.g., paragraph bridging pages 48-49; Figure 9). RTEF-1 overexpression stimulates COX-2 promoter activity over three-fold in BAEC (e.g., page 49, lines 7-21; Figure 11).

There are no working examples of the claimed invention. Example 10 of the specification is a prophetic example directed to the use of a recombinant adenovirus construct to express RTEF-1 in mouse heart to assay the physiological effects of RTEF-1 expression on the relative angiogenic factors *in vivo*. Example 11 of the specification is a prophetic example directed to the *in vivo* delivery of a recombinant adenovirus or adeno-associated virus to patients diagnosed with coronary artery disease or peripheral vascular disease for treatment. The specification envisions increasing neovascularization or angiogenesis in these patients by inducing VEGF, FRGFR1, and COX-2 expression in vascular endothelial cells. Example 12 is a prophetic example directed to combination therapy using RTEF-1 and HIF-1α.

The use of RTEF-1 to stimulate VEGF, FGFR1 and COX-2 expression in endothelial cells is the basis for the claimed invention (e.g., page 23, lines 8-11). The specification teaches that VEGF is one of the most promising angiogenic ligands targeted in the art for therapeutic purposes. VEGF receptors are typically upregulated under ischemic conditions and the administration of recombinant VEGF has been shown to augment the development of collateral vessels and improve the function of peripheral and myocardial ischemic tissues (e.g., page 1, lines 15-30). Further, the specification teaches that FGF is a potent endothelial cell mitogen which increases the survival and proliferation of endothelial cells (e.g., paragraph bridging pages 1-2). The specification teaches that COX-2 is another factor involved in normal angiogenesis, as wells as tumor-associated angiogenesis (e.g., page 2, lines 3-6).

The specification asserts that RTEF-1 can be useful to treat, reduce or prevent conditions caused by hypoxia, and can be used to promote angiogenesis by increasing blood vessel growth in a mammal (e.g., page 2, line 21 to page 3, line 8). The specification envisions the treatment,

reduction or prevention of ischemic conditions including cardiac infarction, chronic coronary ischemia, chronic lower limb ischemia, stroke, cerebral ischemia, peripheral vascular disease, myocardial ischemia, myocardial infarcts, unstable angina, cardiac hypertrophy, arrhythmia, cardiomyopathy, angina pectoris, atherosclerosis, arteriosclerosis, a complication of diabetes, restenosis, organ hypertrophy, organ hyperplasia, septic shock, inflammatory disease, and myocardial dysfunction (e.g., page 4, lines 22-29; paragraph bridging pages 24-25). The specification envisions the prophylactic use of RTEF-1 in the anticipation of an ischemic condition, such as with a surgical procedure or trauma (e.g., paragraph bridging pages 4-5; page 26, lines 1-11).

With regard to the administration of RTEF-1 protein, the specification envisions the use of cell therapy methods such as microinjection or transduction. The specification envisions using local or systemic administration (e.g., page 25, lines 15-19). The specification defines "RTEF-1" to mean any polypeptide that exhibits an activity common to its related, naturally occurring RTEF-1 polypeptide. Thus, the specification envisions using any amino acid sequence with RTEF-1 activity. The claims require at least 60% or at least 80% identity to Accession Numbers AAC50763, Q62296 or P48984 (e.g., page 14, lines 21-27); however, the specification only teaches the sequence of AAC50763 (SEQ ID NO: 7). At page 9, lines 24-32, the specification states the following with regard to determining angiogenic activity:

> Angiogenic activity may be determined in *vitro* by measuring, for example, endothelial cell proliferation, endothelial cell migration, endothelial cell survival, and tubule formation. Alternatively, angiogenic activity may be determined in *vivo,* by counting or staining vessels, or alternatively, by quantitating functional vessels, using the MATRIGEL® assay, corneal micropocket assay, hind limb ischemic model, and chick chorioallantoic membrane (CAM) assay. Preferably, in *vitro* assays measure endothelial cell proliferation or survival and preferred *in vivo* assays are the hind limb ischemic model and the corneal micropocket assay.

For the purpose of determining claim scope, the preferred assay is hind limb ischemic model.

With regard to the administration of a nucleic acid molecule encoding RTEF-1, the specification envisions the use of a plasmid vector or a viral vector, where the viral vector is an adenovirus, retrovirus, adeno-associated virus, herpes simplex virus, SV40, polyoma virus, papilloma virus, picornavirus, or vaccinia virus (e.g., page 4, lines 13-17). The specification envisions using a tissue-specific promoter to direct expression of RTEF-1 in endothelial cells, cardiomyocytes, skin cells, hepatocytes, myocytes, adipocytes, fibroblasts, or any tissue (e.g., page 4, lines 17-21; page 36, line 28 to page 37, line 25). The specification envisions using local or systemic administration (e.g., page 25, lines 15-19). General techniques regarding the *in vivo* or *ex vivo* administration of nucleic acid are discussed at page 28, line 30 to page 30, line 2 and page 31, line 11 to page 32, line 25).

Predictability and state of the art: The present invention is based upon the use of RTEF-1 to activate the transcription of genes such as VEGF. The specification teaches that the systemic administration of VEGF can cause the promiscuous induction of angiogenesis in healthy host tissues and cause blindness, increase the aggressiveness of tumor cells, and lead to a multitude of negative side-effects (e.g., page 2, lines 7-16). Thus, it would be unpredictable to systemically administer RTEF-1 polypeptide or nucleic acid, which would result in the systemic activation of VEGF expression.

It would be unpredictable to use a chick RTEF-1 protein to treat a mammal to increase angiogenesis or reduce hypoxia. The chick protein would be expected to be functional in chick; however, the claims are limited to the use of the chick RTEF-1 protein and nucleic acid in a mammal. There is no evidence on the record that demonstrates the ability of the non-mammalian

chick protein to function to stimulate VEGF, FGFR1 and COX-2 expression in a mammalian cell. One has no knowledge of whether the conserved residues in the human and chick proteins, for example, are sufficient to confer such function.

It would be unpredictable to use the RTEF-1 polypeptides and nucleic acid molecules to prevent hypoxia. As discussed in the specification, RTEF-1 protein activates the expression of VEGF. Angiogenesis may be mediated by increasing VEGF expression. The specification teaches the use of VEGF protein to stimulate angiogenesis (e.g., page 2). The art teaches the safe and effective use of VEGF gene therapy to treat hypoxia or stimulate angiogenesis (see Gupta et al. Circulation Research, Vol. 105, No. 8, pages 724-736, October 2009 for a review of the literature). Although some beneficial therapeutic effect may be obtained, there is no evidence that the effects of hypoxia may be prevented by RTEF-1.

It would be unpredictable to use any polyoma vector, papilloma virus vector, or picornavirus vector for gene therapy. Strayer (Journal of Cellular Physiology, Vol. 181, pages 375-384, 1999) teaches that the shortcomings of gene therapy in meeting its goals largely reflect limitations of the vectors that have been used to deliver the gene therapy (e.g., page 375, right column, 2nd paragraph). SV40 is one member of the family of *polyomaviridae* (Ehrhardt et al. Current Gene Therapy, Vol. 8, pages 147-161, 2008; e.g., page 151, left column, 1st full paragraph). The prior art teaches that SV40 vector suitable for gene therapy applications (Strayer, DS. Journal of Cellular Physiology, Vol. 181, pages 375-384, 1999; Strayer et al. Current Opinion in Molecular Therapeutics, Vol. 4, No. 4, pages 313-323, August 2002). Neither the specification nor art of record teach the use of any other polyoma vector for gene therapy. The art does not teach the use of papilloma virus vectors for gene therapy. Ehrhardt et

al teach that bovine papillomavirus (BPV) belongs to the family of *papillomaviridae*, but is not suitable for use in gene therapy applications, because it is known to cause cellular immortalization (e.g., page 151, right column The BPB (Intermediate Copy Number) Plasmid Replicon)). There is no art on the record that indicates it would have been routine in the art at the time the invention was made to make and use papilloma viruses for gene therapy applications. Further, Hewson (Molecular Medicine Today, Vol. 6, pages 28-35, January 2000) teaches that picornaviruses encompass a diverse family of small, non-enveloped, positive-strand RNA virus, and that poliovirus is one member of the family (e.g., page 29, left column). Hewson teaches that poliovirus is attractive as a future recombinant vaccine vector and that the vector is selectively taken up by human mucosal M cells, which are important for antigen sampling of the gut environment (e.g., page 29, left column). The present invention requires the delivery of RTEF-1 polypeptide to cells such as endothelial cells, where the protein alters the expression of angiogenic factors. The present invention is not consistent with using a vector capable of delivering an antigen to stimulate an immune response. There is no evidence on the record that picornaviruses can be used to deliver RTEF-1 to a mammal to stimulate angiogenesis or reduce hypoxia.

Amount of experimentation necessary: The quantity of experimentation required to carry out the full scope of the claimed invention is large. One of skill in the art would first be required to screen a number of RTEF-1 polypeptide variants for angiogenic activity in order to determine which variants encompassed by the claims have the claimed activity. Neither the prior art nor present specification provide specific guidance with regard to the 20% or 40% of the disclosed amino acid sequences that can be altered while retaining function. Because one would have no

knowledge beforehand, it would require a large amount of experimentation to identify variants that have the claimed function. Next one would be required to develop polyoma, papilloma and picornavirus vectors suitable for gene therapy. Then one would be required to determine how to deliver the RTEF-1 polypeptides and polynucleotides in order to provide sufficient expression of angiogenic factors to prevent hypoxia.

In view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention. Therefore, claims 120-122 and 132-134 are not considered to be fully enabled by the instant specification.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 132-134 are rejected under 35 U.S.C. 102(b) as being anticipated by Umezawa et al (US Patent Application Publication No. 2002/0142457 A1; see the entire reference), as evidenced by the entry for TEAD 4 TEA domain family member 4 [*Homo sapiens*], GeneID: 7004, printed from Entrez Gene on 10/23/2009 as pages 1/7 to 7/7.

The claims encompass a method of treating or reducing hypoxia in a mammal at risk for or experiencing hypoxia, comprising providing to said mammal a therapeutically effective amount of a nucleic acid molecule encoding Related Transcriptional Enhancer Factor-1 (RTEF-

1), where the RTEF-1 protein has at least 80% sequence identity to the sequence of human RTEF-1 (Accession Number AAC50763), which is disclosed as SEQ ID NO: 7 in the present specification. Claim 133 limits the nucleic acid molecule to an expression vector selected from the group consisting of a plasmid or a viral vector, and claim 134 limits the viral vector to one such as an adenovirus, retrovirus, or adeno-associated virus. The present specification discloses that hypoxia is a central feature of pathological conditions involving abnormal vascularization, such as myocardial infarction (e.g., paragraph bridging pages 22-23).

Umezawa et al teach the treatment of heart diseases such as myocardial infarction comprising locally administering a recombinant virus vector encoding TEF-3 to the myocardium using a catheter or the like so that the virus can be absorbed into the myocardium of the patient (e.g., paragraphs [0150]-[0152], [0158]-[0160], [0165]-[0178]). Umezawa et al teach the method where the virus vector is an expression vector (e.g., paragraphs [0169] and [0175]). Umezawa et al teach the method where the recombinant viral vector is a retrovirus, lentivirus, adenovirus, or adeno-associated virus (e.g., paragraphs [0167]-[0172]). Umezawa et al teach the method where TEF-3 encoding nucleic acid molecule has the sequence of SEQ ID NO: 28, which encodes the protein of SEQ ID NO: 27 (e.g., paragraph [0165]).

The sequence of Umezawa et al is at least 80% identical to the amino acid sequence of Accession No. AAC50763 (see the attached alignment in Appendix I). The Entrez Gene entry for TEAD 4 TEA domain family member 4 is cited only to show that RTEF-1 is also known as TEF-3 (e.g., page 1/7). Because the TEF-3 protein of Umezawa et al is an RTEF-1 protein, it would necessarily have angiogenic activity.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jennifer Dunston/
Examiner
Art Unit 1636